DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Mr. Rick Leber
Regulatory Manager
Abbott Laboratories
200 Abbott Park Road
Abbott Park, IL 60064-6157

RE: NDA # 18-723, 21-168
Depakote® (divalproex sodium delayed-release) Tablets
Depakote® ER (divalproex sodium extended-release) Tablets
MACMIS # 16146

Dear Mr. Leber,

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a Depakote ER/Depakote Continuum Care Pharmacy Formulary Flashcard (744-160303) (Flashcard) for Depakote® (divalproex sodium delayed-release) Tablets (Depakote) and Depakote® ER (divalproex sodium extended-release) Tablets (Depakote ER) submitted under cover of Form FDA-2253 by Abbott Laboratories (Abbott). The Flashcard is misleading because it omits risk information for Depakote and Depakote ER, broadens the indication of Depakote ER, omits indication information for Depakote, and omits material information about Depakote ER. Thus, this promotional material misbrands the drugs in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) and 321(n). *Cf.* 21 CFR 202.1(e)(3)(i); (e)(3)(ii); (e)(6)(i) & (e)(6)(ii).

Background

According to its FDA-approved product labeling (PI), Depakote is indicated, among other things, for the following (in pertinent part):

> **Mania**
> DEPAKOTE . . . is indicated for the treatment of the manic episodes associated with bipolar disorder . . . .
>
> The safety and effectiveness of DEPAKOTE for long-term use in mania, i.e., more than 3 weeks, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use DEPAKOTE for extended periods should continually reevaluate the long-term usefulness of the drug for the individual patient.

Epilepsy
DEPAKOTE . . . is indicated as monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures. DEPAKOTE . . . is also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types that include absence seizures.

According to its FDA-approved PI, Depakote ER is indicated, among other things, for the following (in pertinent part):

Mania
DEPAKOTE ER is indicated for the treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features . . . .

The safety and effectiveness of valproate for long-term use in mania, i.e., more than 3 weeks, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use DEPAKOTE ER for extended periods should continually reevaluate the long-term risk-benefits of the drug for the individual patient.

Epilepsy
DEPAKOTE ER is indicated as monotherapy and adjunctive therapy in the treatment of adult patients and pediatric patients down to the age of 10 years with complex partial seizures that occur either in isolation or in association with other types of seizures. Depakote ER is also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures in adults and children 10 years of age or older, and adjunctively in adults and children 10 years of age or older, and adjunctively in adults and children 10 years of age or older with multiple seizure types that include absence seizures.

The use of Depakote and Depakote ER is associated with a number of serious risks. The PIs for both products include Boxed Warnings for hepatotoxicity (resulting in **fatalities**), teratogenicity (such as neural tube defects), and pancreatitis (life-threatening cases have been reported). Both drugs are contraindicated in patients with hepatic disease or significant hepatic dysfunction, in patients with known hypersensitivity to the drug, and in patients with known urea cycle disorders. In addition to these Boxed Warnings, the Warnings and Precautions section for Depakote ER and the Warnings and Precautions sections for Depakote disclose numerous additional risks, including somnolence in the elderly, thrombocytopenia, hyperammonemia, hyperammonemia and encephalopathy associated with concomitant topiramate use, multi-organ hypersensitivity reactions, and suicidal ideation, as well as cautions regarding drug plasma monitoring, effects on ketone and thyroid function tests, and effects on HIV and CMV viruses replication. In addition, the PI for Depakote ER contains a warning related to hypothermia. Depakote and Depakote ER are also associated with a number of common adverse reactions for both their mania and epilepsy indications.

According to the DOSAGE AND ADMINISTRATION section of the Depakote ER PI (in pertinent part):

Conversion from DEPAKOTE to DEPAKOTE ER
In adult patients and pediatric patients 10 years of age or older with epilepsy previously receiving Depakote, Depakote ER should be administered once-daily using a dose 8 to 20% higher than the total daily dose of Depakote (Table 1). For patients whose Depakote total daily dose cannot be directly converted to Depakote ER, consideration may be given at the clinician's discretion to increase the patient's Depakote total daily dose to the next higher dosage before converting to the appropriate total daily dose of Depakote ER.

Table 1. Dose Conversion

Depakote Total Daily Dose (mg)	Depakote ER (mg)
500* - 625	750
750* - 875	1000
1000*-1125	1250
1250-1375	1500
1500-1625	1750
1750	2000
1875-2000	2250
2125-2250	2500
2375	2750
2500-2750	3000
2875	3250
3000-3125	3500

* These total daily doses of DEPAKOTE cannot be directly converted to an 8 to 20% higher total daily dose of DEPAKOTE ER because the required dosing strengths of DEPAKOTE ER are not available. Consideration may be given at the clinician's discretion to increase the patient's DEPAKOTE total daily dose to the next higher dosage before converting to the appropriate total daily dose of DEPAKOTE ER.

In addition, according to the CLINICAL PHARMACOLOGY section of the Depakote ER PI (in pertinent part):

Pharmacokinetics
Absorption/Bioavailability
When given in equal total daily doses, the bioavailability of DEPAKOTE ER is less than that of DEPAKOTE (divalproex sodium delayed-release tablets) . . . .

After multiple once-daily dosing of DEPAKOTE ER, the peak-to-trough fluctuation in plasma valproate concentrations was 10-20% lower than that of regular DEPAKOTE given BID, TID, or QID.

Conversion from DEPAKOTE to DEPAKOTE ER:
When DEPAKOTE ER is given in doses 8 to 20% higher than the total daily dose of DEPAKOTE, the two formulations are bioequivalent.

Pharmacodynamics
The relationship between plasma concentration and clinical response is not well documented.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The Flashcard is misleading because it presents numerous efficacy claims for Depakote and Depakote ER, but fails to include **any** risk information in the body of the Flashcard. As described above, there are numerous risks associated with the use of Depakote and Depakote ER, including risks described in boxed warnings and contraindications, as well as other warnings, precautions, and adverse reactions.

The statement, "Please see . . . Important Safety Information including Boxed Warnings . . . on reverse side" included in small type in the lower left-hand corner of the Flashcard does not mitigate this misleading presentation. As a result, the Flashcard misleadingly suggests that Depakote and Depakote ER are safer than has been demonstrated.

Broadening of Indication/Omission of Indication

The Flashcard is misleading because it implies that Depakote ER is indicated for use in a broader range of mania patients than Depakote, when this is not the case. Specifically, the Flashcard includes the following claim (emphasis added):

- "**Expanded** acute mania indication with Depakote ER that includes mixed episodes associated with bipolar disorder, with or without psychotic features"

This statement misleadingly suggests that Depakote ER is indicated for a broader mania population than Depakote. In fact, the populations studied in the mania clinical trials of both products were selected using a broad interpretation of acute mania in bipolar disorder, and as described in the PIs for both products, there were no clinical differences between the mania populations studied for each drug. The implication that the mania indication for Depakote ER is an "expanded" indication that offers an advantage over Depakote is misleading. The differences in the wording of the mania indications for the two drugs are merely a reflection of the different DSM criteria that were in effect at the time of the drugs' approvals, and not a reflection of an "expanded indication" for Depakote ER. Specifically, when Depakote was approved in 1983, DSM III-R[1] criteria were used (which placed less emphasis on subtype categorization), and when Depakote ER was approved in 2000, DSM-IV TR[2] criteria were used (which delineated the various subtypes).

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[1] Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised.
[2] Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.

Additionally, we note that the Flashcard fails to include specific indications for Depakote. The statement, "Please see full Indications . . . on reverse side" in small type in the bottom left-hand corner of the Flashcard does not mitigate this omission.

Omission of Material Facts

The Flashcard is misleading because it omits material contextual information regarding the clinical pharmacology of Depakote ER. Specifically, the Flashcard presents the claim, "**Smoother blood levels** with fewer peaks and troughs" (emphasis added). We acknowledge the statement in the CLINICAL PHARMACOLOGY, Pharmacokinetics section of the Depakote ER PI that ". . . the peak-to-trough fluctuation in plasma valproate concentrations was 10-20% lower than that of regular DEPAKOTE given BID, TID, or QID." However, the CLINICAL PHARMACOLOGY, Pharmacodynamics section of the Depakote ER PI also states that "[t]he relationship between plasma concentration and clinical response is not well documented." By presenting the claim "smoother blood levels" without revealing the material contextual information from the PI that the clinical significance of this is not well documented, the Flashcard misleadingly suggests that Depakote ER use will offer patients some clinical benefit due to "smoother blood levels," when this has not been demonstrated.

Furthermore, the Flashcard claims that Depakote ER has "**All the Benefits of Depakote With the Advantages of Extended Release**" (emphasis in original). This claim is misleading because it omits important contextual information regarding the clinical pharmacology of Depakote ER. Specifically, Depakote ER is not bioequivalent to Depakote at equal daily doses. Rather, as reflected in the CLINICAL PHARMACOLOGY, Pharmacokinetics section of Depakote ER's PI, Depakote ER is 8-20% less bioavailable when compared to equal daily does of Depakote. Therefore, to obtain an equivalent bioavailable dose of Depakote, the Depakote ER dose must be increased by 8-20%. (See Table 1 in the Background section above for conversion dosing of Depakote to Depakote ER.) By failing to include this material contextual information, the Flashcard misleadingly suggests that Depakote ER offers all of the benefits of an equal dose of Depakote, when this is not the case.

Conclusion and Requested Action

For the reasons discussed above, the Flashcard misbrands Depakote and Depakote ER in violation of the Act, 21 U.S.C. 352(a) and 321(n). *Cf.* 21 CFR 202.1(e)(3)(i); (e)(3)(ii); (e)(6)(i) & (e)(6)(ii).

DDMAC requests that Abbott immediately cease the dissemination of violative promotional materials for Depakote and Depakote ER such as those described above. Please submit a written response to this letter on or before February 6, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for Depakote and Depakote ER as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705, facsimile at (301) 847-8444. In all future

correspondence regarding this matter, please refer to MACMIS #16146 in addition to the NDA numbers. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Depakote and Depakote ER comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Amy Toscano, Pharm.D., CPA
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amy Toscano
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